REMARKS

Entry of the foregoing amendments, reconsideration and re-examination of the subject application, as amended, pursuant to and consistent with 37 C.F.R. §1.112, and in light of the remarks which follow, are respectfully requested.

By the present amendments, the previous claims have been cancelled in favor of new Claims 21-40, all of which correspond to the elected invention, namely treatment of an autoimmune disease (psoriasis elected) by administration of antibodies to B7.1 (CD80) having the epitopic specificity of the three exemplified anti-B7 antibodies 7C10, 7B6 and 16C10 having the nucleic acid and amino acid sequences respectively contained in SEQ ID NO:1-4; 5-8; and 9-12. The present claims broaden the scope of the previous claims at least in the fact that the claims are not restricted to use of primatized antibodies.

Turning now to the Official Action, Applicants have noted the formality objections. The title and specification have respectively been revised to include the patent number and to be more descriptive of the elected subject matter as suggested by the Examiner. Withdrawal of the objections is respectfully requested.

Also, the Examiner is advised that formal figures will be provided upon allowance.

Previous claims 16-19 stand rejected as not being enabled. This rejection is respectfully traversed.

Essentially, the Examiner questions whether antibodies to B7.1 (CD80) which inhibit the interaction of CD28 and B7 (e.g. CD80) will mediate a therapeutic effect that will correlate to the effective treatment of autoimmune diseases and specifically psoriasis. In support of this rejection, the Examiner questions whether the antibody will reach the requisite target, will exhibit appropriate functional properties, and that unknown effects that may cause adverse effects *in vivo* may be present.

In further support of this rejection, the Examiner relies on various references. The position of the Examiner is respectfully traversed in view of the foregoing.

Foremost, with respect to the Kahan reference, it is noted that the Patent Office has already accepted (based on the issuance of U.S. Patent No. 5,885,579) that ligands to B7 antigens, including B7.1, may be used in therapeutic methods wherein inhibition, e.g. of the interaction of a B7 antigen with CD28, is therapeutically desirable. The Examiner is referred especially to claims 4 and 5 of the '579 patent. Indeed, in making the rejection, the Examiner is seemingly improperly raising doubts as to the validity of an issued U.S. patent. While the

undersigned is aware that the patentability of each application may raise different issues, certainly the subject application contains more functional data in support of the efficacy of the claimed method than does the '579 patent. Accordingly, the rejection is respectfully submitted to be unsustainable. Also, with further respect to the Kahan reference, it is not germane to the claimed invention as it does not relate to the efficacy of anti-B7.1 (CD80) antibodies as therapeutics. Rather, it is predominantly relating to another antibody (anti-CD3) and its alleged adverse side effects. Whether one antibody elicits side effects is not reasonably prohibitive of another, especially one that binds to a distinct target.

Secondly, with further respect to the disclosed *in vitro* assays, it is respectfully submitted that this information is probative of the efficacy of the claimed methods. In particular, Applicants have demonstrated that anti-B7.1 antibodies having the claimed epitope specificity bind B7 expressing cells, and also that B7 specifically interacts with activated T cells, and that this interaction is effectively blocked by the use of antibodies having the claimed epitopic specificity (see Examples 6 and 7, respectively). Also, the subject application contains *in vitro* data establishing that antibodies having the claimed epitope specificity effectively inhibit IL-2 levels. Applicants respectfully submit that this is an accepted assay for the efficacy of potential *in vivo* immunosuppressants.

With respect to the foregoing, it is well known that activated T cells are involved in the pathology of a variety of autoimmune diseases, including psoriasis. In support of this fact, Applicants refer the Examiner's attention to U.S. Patent 6,162,432, a patent assigned to Biogen, which this same Examiner issued. Therein is claimed a method of treating skin diseases, including psoriasis, by administration of antibodies which inhibit the LFA-3/CD2 interaction, thereby inhibiting activated T cell activation and/or proliferation. Also, other patents have issued directed to treatment of other autoimmune diseases, using such antibodies, based on their ability to inhibit T cell activation and/or proliferation.

Hence, the same Examiner has acknowledged that some autoimmune diseases, including psoriasis, may be treated by use of antibodies that inhibit activated T cells. It is respectfully submitted that targeting the instant B7.1 binding antibodies to the requisite target (psoriatic lesions) should be no more problematic with anti-B7.1 antibodies than with anti-CD2 antibodies. Moreover, as the subject antibodies target B cells rather than T cells, the risk for adverse side effects is not as significant as with anti-CD2 antibodies.

Also, the Examiner's reliance on the Blazar et al., Perrin et al., Daikh et al. and other references is respectfully traversed. Essentially, these references are cited in an attempt to establish the problems and unpredictability in the use of antibodies to B7 antigens to treat autoimmune or other diseases, including GVHD, diabetes, and multiple sclerosis (EAE model thereof).

First, it is respectfully submitted that these references do not disclose any problems with treatment of psoriasis using antibodies to B7.1. Also, it is respectfully submitted that the concerns relating to the antibodies of the references cannot be analogized to the antibodies of the present invention. They cannot because, unlike the antibodies of the references, the subject antibodies do not inhibit the interaction of CTLA-4 and B7.1 antigen. Rather, antibodies possessing the recited epitopic specificity selectively only inhibit the interaction of B7.1 antigen and CD28.

Therefore, any adverse side effects observed with the antibodies of the references cannot be reasonably assumed to be inherent to the subject antibodies. (It should be noted that the failure of antibodies of the present invention to inhibit CTLA-4/B7.1 interaction is established by information contained in a later-filed U.S. application, Serial No. 08/746,361, also being examined by the subject Examiner. It is clear from this application that the argued binding differences are inherent to anti-B7.1 (CD80) antibodies that possess the recited epitopic specificity).

Also, Applicants respectfully advise that the Examiner's enablement concern with respect to the redundancy of B7.1 and B7.2 on B cells, and their co-stimulatory effect on the immune system also does not suggest the non-efficacy of the subject antibodies. Particularly, Applicants respectfully submit that there is no reason to believe that the disclosed in vitro assays (discussed supra) will not correlate to the in vivo efficacy of the subject antibodies to suppress autoimmunity. In support of this argument, Applicants provide an abstract from Liu et al., *Digestive Disease Week* (May 21-24, 2000) San Diego, CA, p. A583, that establishes the efficacy of an anti-CD80 (B7.1) antibody to block autoimmune responses in an animal model of colitis, whereas anti-CTLA-4 and anti-CD86 antibody treated mice still developed the disease. This provides additional support as to why antibodies having the recited specificity (selective for B7.1 but which do not inhibit CTLA-4/B7 interaction) should be effective in mice.

Still further, Applicants respectfully advise that they have Phase I clinical data which provides in vivo data in support of the safety and efficacy of the invention antibodies for treating autoimmune disease, particularly psoriasis. This data will be provided to the Examiner shortly.

Also, it is respectfully submitted that it is incumbent upon the Patent Office to substantiate a §112 non-enablement rejection. Applicants respectfully submit that this burden has not been met as no evidence is of record which would suggest that the recited antibodies will not be therapeutically effective, especially in the context of treatment of psoriasis.

Finally, with respect to the deposit-based rejection, the independent claim now provides that the recited antibodies possess specific primatized variable heavy and light sequences. Therefore, practice of the claimed invention does not require deposit as the requisite sequences are provided.

Therefore, based on the foregoing, withdrawal of the §112 , first paragraph, rejection as it may apply to the newly submitted claims is respectfully requested.

Claim 17 (now cancelled) was previously rejected on §112 indefiniteness issues. This rejection is respectfully traversed on the basis that the new claims make the intent clear of the recited antibody designations clear based on their referral to specific sequence number identifiers.

Claims 16 and 18-19 stand rejected under 35 U.S.C. §102(e) based on Linsley et al.

This rejection is not applicable to the current claims as Linsley et al. does not teach the use of any antibodies having the recited epitopic specificity for treatment of autoimmunity in general or psoriasis specifically. Also, the rejection was not applicable to the previous claims as the reference fails to teach primatized antibodies specific to B7.

Claims 16 and 18-19 further stand rejected under 35 U.S.C. §103 based on Linsley et al. and Nickoloff et al. This rejection is also respectfully traversed.

In particular, Linsley does not anticipate nor render obvious the use of anti-B7.1 antibodies possessing the recited epitopic specifically. Nor are the subject antibodies equivalent to the antibodies described by Linsley et al. This is apparent based on references cited in the Official Action herein.

Specifically, Perrin et al. teaches that the administration of CTLA-4 Ig effectively treated EAE (apparently based on its interaction with CTLA-4 and B7 antigen). By contrast, the subject antibodies do not inhibit the interaction of B7 and CTLA-4. However, it cannot

be assumed, indeed it would be improbable to expect that an antibody to B7.1 which selectively inhibits the B7.1/CD28 interaction will behave equivalently to an antibody to B7.1 that inhibits a different interaction [vis-à-vis the Linsley et al. anti-B7.1 antibody (BB1)].

Further, the Liu abstract discussed above shows the non-equivalency of antibodies to CTLA-4 and B7.1 for treating autoimmunity.

Also, it should be emphasized that this line of argument does not contradict the rebuttal to the lack of enablement rejection. While the subject antibodies will not block the equivalent immune pathway as the reference antibody, efficacy is established based on the *in vitro* data which shows that the subject antibodies inhibit the interaction of B7+ (e.g. B cells) with activated T cells. As activated T cells are well known to be involved in the pathology of psoriasis, this information is probative of the efficacy of the claimed therapeutic methods.

Turning now to Nickoloff et al., it is noted that this reference suggests that B7.1 is upregulated on lymphocytes of chronic skin disorders including psoriasis. However, this does not render the claimed therapeutic methods obvious as there is no disclosure that B7.1 levels actually correlate to disease pathology. Essentially, it is not reported that the overexpression actually contributes to the disease symptoms.

Also, Applicants respectfully advise that they have obtained in vitro data (attached to this Reply) wherein the effects of the Nickoloff et al. antibody to the subject antibody were compared in a mited lymphocyte reaction wherein the subject antibody effectively inhibited IL-2, but the Nickoloff et al. antibody (L307) did not. Thus, the effects of the subject antibody cannot be analogized to Nickoloff et al.

Also, as with the primary references, Nickoloff et al. is further deficient in that it likewise fails to teach or suggest the use of antibodies having the recited epitopic specificity as a therapeutic, particularly for treatment of psoriasis.

Therefore, based on the foregoing, it is respectfully submitted that Linsley et al. and Nickoloff et al., separately or in combination, do not anticipate or render obvious the claimed therapies.

In view of the foregoing, the claims are now believed to be in form for allowance, and such action is hereby solicited. If any points remain in issue which the Examiner feels may be best resolved through a personal or telephone interview, he is kindly requested to contact the undersigned at the telephone number listed below.

Attached hereto is a marked-up version of the changes made to the specification and claims by the current amendment. The attached Appendix is captioned **"Version with markings to show changes made"**.

All objections and rejections having been addressed, it is respectfully submitted that the present application is in a condition for allowance and a Notice to that effect is earnestly solicited.

Respectfully submitted,

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APPENDIX: VERSION WITH MARKINGS TO SHOW CHANGES MADE

IN THE SPECIFICATION:

Page 1, first paragraph under the heading "Cross Reference to Related Applications", please delete the current paragraph and insert the following new paragraph:

--This application is a divisional of Application No. 08/487,550, filed June 7, 1995, now U.S. Patent 6,113,898.--

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BLOCKADE OF CD28/CTLA-4-B7 COSTIMULATORY PATHWAY IN COLITIC SCID MICE.

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Background/Aims: CD28/B7 (CD80/CD86) interaction is important for inducing T cell activation, while CTLA-4-B7 interaction seems to play a role in down-regulating immune responses. CD28 signaling plays a role in some autoimmune diseases. B7 expression is increased in inflamed mucosa of inflammatory bowel disease, while its exact role in the pathogenesis is still unknown. In this study, blockade of B7 and CTLA-4 was utilized to investigate the in vivo relevance of B7-CD28/CTLA-4 interaction in colitic SCID mice. Methods: Colitis was induced in SCID mice by reconstitution with syngeneic CD45RBhigh CD4+ T cells. These mice were injected intraperitoneally with either anti-CD80 or anti-CD86 or anti-CTLA-4 or control IgG (250 μg) twice weekly, from the beginning of T cell reconstitution over an 8 week period. The clinical manifestations were monitored weekly. Mice were sacrificed after 8 weeks for histological analysis and cytokine production. Infiltration of leukocytes and CD54 expression in the colon was examined by immunohistochemistry. Results: Colitic SCID mice treated with anti-CTLA-4 developed progressive weight loss already 2 weeks after transfer. These mice had more severe colitis compared with control IgG-treated recipients, with diarrhea and increased mucus in the stool by 4-5 weeks. Anti-CD80-treated mice showed a significant clinical and histological improvement with slight weight loss and adsence of diarrhea. Histological analysis of colonic sections revealed significantly diminished leukocyte infiltration and epithelial hyperplasia, and decreased infiltration of CD4+ T cells, F4/80 macrophages and CD54 expression. Lamina propria CD4+ T cells, when stimulated with coated anti-CD3ε and mouse CD80 transfectants, produced lower levels of IL-2 and IFN-γ compared with controls. Anti-CD86-treated mice still developed colitis with no clinical or histological difference between this group and controls, showing weight loss at 4-5 weeks and diarrhea at 6-8 weeks. Transmural inflammation was seen in all colonic samples. Epithelial lesions included loss of goblet cells, crypt abscesses, and ulcerations. Conclusions: B7 costimulatory pathway is involved in intestinal mucosal inflammation. Lake of CTLA-4 triggering might be important in maintenance of inflammation. Blockade of B7 signaling, especially CD80 sigaling, may be beneficial for Crohn's disease.

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L307.4 anti-CD80 used in published Nickoloff experiment is shown below with two lots of IDEC-114 and negative control IgG human antibody RF2. CTLA-4Ig which blocks both B7-1 and B7-2 interactions with CD28 is used as a positive control. Multiple experiments have shown no significant inhibitory effects of L307.4 where IDEC-114 blocks effectively IL-2 production in this assay where B7-2 is also present. These results confirm the two anti-CD80 antibodies have different mechanisms and functional properties. These properties are unique to the Primatized antibodies IDEC-114 (P16C10) and P7C10 claimed in the patent.

The Effect of IDEC-114 on IL-2 Production of Human PBMC MLR Assay